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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff v. GENENCOR INTERNATIONAL, INC. and ENZYME DEVELOPMENT CORPORATION Defendants	C.A. No. 05-160-KAJ

MEMORANDUM OF LAW IN SUPPORT OF
PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION

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I. NATURE AND STAGE OF THE PROCEEDINGS

This is a patent infringement action. Plaintiff Novozymes A/S ("Novozymes") filed its complaint on March 15, 2005, asserting infringement of its U.S. Patent No. 6,867,031 ("the '031 patent"). Defendants Genencor International, Inc. and Enzyme Development Corporation[1] (collectively "Genencor" or "Defendants") have answered, denying infringement and asserting affirmative defenses of invalidity and unenforceability of the '031 patent.

II. PRELIMINARY STATEMENT

Plaintiff Novozymes seeks preliminary injunctive relief to return to and maintain the *status quo* and thus immediately halt the irreparable harm caused to Novozymes by Genencor. Genencor is selling to the domestic fuel ethanol industry an industrial enzyme product (called Spezyme® Ethyl) that incorporates Novozymes' patented technology in direct competition with Novozymes' market-leading industrial enzyme product (Liquozyme® SC). Sale of Genencor's Spezyme Ethyl product literally infringes Novozymes' '031 patent (Attached as Exhibit A).

The '031 patent covers improved industrial enzymes, called alpha-amylases, that are important for the commercial conversion of corn and other crops to fuel ethanol. Fuel ethanol is used as an environmentally-friendly supplement to gasoline to help reduce reliance on imported oil. Not surprisingly, the demand for fuel ethanol has skyrocketed as petroleum prices have reached historically high levels.

Novozymes' patented Liquozyme® SC alpha-amylase, which it introduced to the U.S. market in 1999, had developed a domestic market share of about [redacted]% (by sales) before

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[1] Enzyme Development Corporation ("EDC") is a United States distributor for Genencor's infringing product.

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Genencor's mid-2004 launch of its "me-too" Spezyme Ethyl alpha-amylase product. Genencor stayed on the market even after it was informed by Novozymes that the allowed patent application (which led to the '031 patent) would cover the Spezyme Ethyl product, and after the '031 patent issued. Since the domestic fuel ethanol market considers Genencor's infringing Spezyme Ethyl product to be interchangeable with Novozymes' market leading Liquozyme SC product, the market share for Liquozyme SC [redacted] because of Genencor's infringing activities.

Lost sales of Liquozyme SC are not the only harm to Novozymes. The fuel ethanol industry uses other enzymes produced by Novozymes, and many customers in the fuel ethanol industry purchase all of their industrial enzyme products from a single supplier. Therefore, Genencor's infringing Spezyme Ethyl product sales have also caused substantial and irreparable harm to Novozymes' sales and market share for related *gluco-amylase* products. This month (June 2005), Genencor was awarded an *annual* contract to supply its infringing Spezyme Ethyl product to a collective of U.S. plants amounting to about [redacted]% of the U.S. fuel ethanol market. Matters will be made worse four months from now (in October 2005), because another annual supply agreement will be awarded covering a different collective of domestic plants amounting to about [redacted]% of the entire United States fuel ethanol market. A third *annual* supply contract covering a collective of domestic plants amounting to about [redacted]% of the U.S. market is traditionally awarded in February. Genencor will have an unfair competitive advantage in the bidding for these contracts if its infringement is not stopped immediately.

Additionally, this unfair competition is ruining Novozymes' reputation as a fair, reliable, and innovative company. Resentment is building among its customers because of what is now

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perceived as over-pricing by Novozymes. However, Novozymes' pricing is what finances its innovation, and its patents are what protect its innovation. If Genencor's infringement continues unfettered, Novozymes will never be able to recover its lost goodwill and customers and will not be able to continue its innovative research.

Finally, Genencor has begun to sell an infringing food grade Spezyme Ethyl product to the food and beverage industry outside of the U.S. and has begun sampling it to this industry in the U.S. Therefore, it is likely that Genencor will soon begin U.S. sales of its food grade infringing product. Novozymes presently sells its patented Termamyl SC alpha-amylase product to this industry. Genencor's sales of its Spezyme Ethyl product to the U.S. food and beverage industry will cause irreparable harm to Novozymes in yet another segment of the commercial enzyme business.

Therefore, immediate injunctive relief is essential to return to the *status quo*. If Genencor's patent infringement is not preliminarily enjoined, Novozymes will suffer irreversible and unfairly precipitated price reductions and loss of market share, for both its Liquozymes SC *alpha-amylase* and related *gluco-amylase enzyme* products, in both the fuel ethanol and food industry markets. This may have a cascading effect, ultimately [redacted] its sole U.S. plant, in Franklinton, North Carolina, that domestically produces its Liquozymes SC product, and where Novozymes is the largest employer (about 400 jobs) and is the main driver of the local economy.

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III. STATEMENT OF FACTS

A. BACKGROUND OF THE TECHNOLOGY AT ISSUE

The '031 patent concerns a type of enzyme called an "alpha-amylase." Arnold Decl. ¶9.[2] Enzymes, including alpha-amylases, are proteins that facilitate biochemical reactions. Alpha-amylases are a specific type of enzyme that catalyzes a chemical reaction to degrade starches into smaller molecules. Arnold Decl. ¶10. Because of this ability, alpha-amylases are useful in a variety of commercial applications that involve the processing of starches -- especially in the fuel ethanol industry, where ethanol fuel is produced from starch crops such as corn, barley, and wheat. Alpha-amylase enzymes are used in this particular industry to liquefy and reduce viscosity of the starch feedstocks, thereby facilitating their processing in the manufacturing plant. In a subsequent step, another industrial enzyme, gluco-amylase (one of which is also made by Novozymes), is used to convert the liquefied starch into fermentable sugars (*e.g.*, glucose). Yeast then converts the sugars into ethanol. LeFebvre Decl. ¶4.[3]

Starch is composed of many smaller glucose sugar molecules, that are joined together by chemical bonds. Alpha-amylase enzymes degrade certain specific chemical bonds, "alpha-1,4-glucosidic bonds," between the many groups of glucose molecules that make up a complex starch molecule, thereby converting complex starch into smaller, simpler groups of glucose molecules. Arnold Decl. ¶10. Commercial alpha-amylase enzymes are typically produced by bacteria. Different bacteria produce different alpha-amylase enzymes which perform the same activity, but vary in certain properties such as their stability at increased temperatures (called

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[2] "Arnold Decl." refers to the Declaration of Frances H. Arnold, Ph.D., dated June 15, 2005, submitted with this memorandum as Exh. B.

[3] "LeFebvre Decl." refers to the Declaration of Gregory K. LeFebvre, dated June 22, 2005, submitted with this memorandum as Exh. D.

"thermostability"). Consequently, different alpha-amylase enzymes may be preferred, depending upon the particular commercial application for which they are used. *Id.*

The '031 patent inventors discovered that altering the structure of a "parent" alpha-amylase enzyme in a specified way produces a "variant" alpha-amylase enzyme that maintains its intended activity, but is much more "thermostable," *i.e.*, remains active at higher temperatures. Because of its high thermostability, this variant alpha-amylase enzyme can be used at high temperatures that normally would significantly reduce the activity of other commercial alpha-amylases. This feature makes the variant alpha-amylase enzymes of the '031 patent particularly desirable in the fuel ethanol industry, where the ability to operate at high temperatures can result in improved efficiency and productivity.

B. PROTEINS AND AMINO ACID SEQUENCES

All proteins, including alpha-amylases and other enzymes, are chains of smaller molecules, called "amino acids," that are joined together by chemical bonds, called "peptide bonds." Arnold Decl. ¶14. There are 20 different amino acids that occur in nature, and each protein chain includes one or more of these 20 amino acids assembled in a particular order. The order of the amino acids in a protein is known as its "amino acid sequence." *Id.*, ¶15.

A protein's individual characteristics are determined by the specific "sequence" of the amino acids in the protein chain. Arnold Decl. ¶19. These characteristics include, for example, the protein's function (*e.g.*, the particular chemical reaction that the protein facilitates), as well as the conditions under which it optimally performs that function. *Id.* Different proteins that have the same or similar function often have similar amino acid sequences. *Id.* For example, alpha-amylase proteins produced by different organisms in nature are similar, by definition, in that they all assist in the same chemical reaction: bond-breaking or "hydrolysis" (*i.e.*, degrading or

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catalyzing the breakdown) of the alpha-1,4-glucosidic chemical bonds in starch. *Id.*, ¶20. Consequently, the alpha-amylase proteins produced by different organisms have similar amino acid sequences. However, their amino acid sequences are usually not identical. *Id.* Differences in the amino acid sequences of different alpha-amylases can give rise to differences in their properties, such as the thermostability discussed above, while retaining the main bond-breaking activity of the alpha-amylase. *Id.*

Scientific nomenclature has assigned a one-letter abbreviation to each of the 20 different amino acids. Hence, the sequence of a particular protein can be specified by writing the one-letter abbreviation for each amino acid in the order that it appears in the protein chain. Arnold Decl. ¶¶15-16. This has been done in Figure 1 of the '031 patent. *Id.*, ¶¶16 and 22. Each of lines 1-4 in that Figure represents the sequence of a different alpha-amylase, using the single-letter abbreviation for each amino acid. *Id.* ¶22. In U.S. patents, both protein sequences and "genetic information" sequences, such as DNA, are typically assigned a unique, consecutive Sequence Identification Number ("SEQ ID NO."), beginning with SEQ ID NO:1, for each different sequence in a given patent. The '031 patent includes several such sequences. Exh. A at 41:1-65:9.[4]

Because the properties of a particular protein are determined by its amino acid sequence, it can be informative when comparing proteins to compare their respective amino acid sequences. Arnold Decl. ¶21. The amino acid sequences are typically "aligned" with one another to achieve the best juxtaposition of individual or groups of amino acids that are common to both proteins. *Id.* The percentage of amino acids in the "aligned sequences" that are either

[4] The convention used herein when citing to a U.S. patent is column:line number(s). For example, 41:1-65:9 refers to column 41, line 1 - column 65, line 9 of the patent.

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identical, or at least chemically similar, can then be determined, and reported as the percent "identity" or "homology," respectively, of the two proteins. *Id.* ¶27; Devereux Decl. ¶12.[5] Figure 1 of the '031 patent illustrates a typical "alignment" of the amino acid sequences of different proteins. Arnold Decl. ¶22. Such an alignment can be performed by eye or, more often, with well-known computer programs. Arnold Decl. ¶21; Devereux Decl. ¶11.

In nature, the proteins produced by a living organism are determined by that organism's genes. Arnold Decl. ¶28. Each protein is "encoded" by a gene specifying that particular protein's amino acid sequence. *Id.* However, those genetic instructions can be manipulated, using genetic engineering, to specify a "variant" of the "parent" protein that is normally produced. *Id.*, ¶¶33-35. The amino acid sequence of a variant protein can differ from that of the parent protein from which it is derived, *e.g.*, by the addition, deletion, or substitution of one or more amino acids in its sequence. *Id.*, ¶35.

C. NOVOZYMES IS A COMPANY DEDICATED TO INNOVATION

Novozymes is an international leader in the research, development, and marketing of commercial enzymes. Its facility in Franklinton, N.C., opened in 1979, is the largest manufacturing plant for industrial enzymes in the U.S. Since 1990, Novozymes has spent over $150,000,000 on plant expansions at that facility. LeFebvre Decl. ¶ 21. Novozymes presently plans future [redacted]. The Franklinton facility includes a research laboratory and a pilot plant, where new enzymes and uses for enzymes are discovered and

[5] "Devereux Decl." refers to the Declaration of John R. Devereux, Ph.D., dated June 11, 2005, submitted with this memorandum as Exh. C.

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developed. Much of this research is directed at solving problems brought to Novozymes by customers. *Id.* ¶22.

Novozymes has built a reputation through innovation and has protected its innovations through patents. If Novozymes could not protect its proprietary technology in the U.S. through patents, it would not have invested as heavily in its research or facilities in the U.S. and will not continue to invest in this manner. LeFebvre Decl. ¶23.

Franklinton consists mainly of farms and small businesses. Novozymes is Franklinton's largest employer, and most of Franklinton's businesses depend in some part on Novozymes and its employees. LeFebvre Decl. ¶24.

D. NOVOZYMES PRODUCES AND SELLS ALPHA-AMYLASE ENZYMES IN THE UNITED STATES

Novozymes produces and sells several enzyme products in the United States which are important to the fuel ethanol industry. Novozymes' Liquozyme® SC and Termamyl® are each *alpha-amylase* products which reduce starch viscosity by breaking complex starches into smaller molecules. Novozymes' Spirizyme® Fuel products are *gluco-amylases* which convert the less viscous, smaller liquefied starches to even smaller glucose molecules which yeast ferment into ethanol. Before Genencor introduced its infringing Spezyme Ethyl alpha-amylase enzyme product in 2004, these Novozymes' enzyme products had gained wide-market acceptance. Novozymes also produces and sells its patented Termamyl SC alpha-amylase product to the food and beverage industry. It is used to break down starches into smaller sugars in this industry, as well. LeFebvre Decl. ¶5.

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E. THE '031 PATENT-IN-SUIT

On March 15, 2005, the '031 patent entitled "Amylase Variants" (Exh. A), issued to Novozymes with five claims to certain "variant" alpha-amylase enzymes. In the underlying motion, Novozymes asserts only independent claims 1 and 3 of the '031 patent to simplify and expedite its preliminary injunction motion. Claim 1 is directed to a variant of a parent *Bacillus stearothermophilus*[6] alpha-amylase. The variant alpha-amylase has an amino acid sequence having at least 95% homology to the parent alpha-amylase, and having a deletion of two particular amino acids: numbers 179 and 180 (using a reference sequence, SEQ ID NO:3, for numbering purposes only). Claim 3 is also directed to a variant alpha-amylase enzyme having alpha-amylase activity and a deletion of the same two amino acids 179 and 180, but having at least 95% homology to the protein sequence set forth in the patent as SEQ ID NO:3.

F. GENENCOR'S INFRINGING PRODUCT

According to Genencor's own description, its "SPEZYME® ETHYL enzyme contains a thermostable starch hydrolyzing [alpha]-amylase ... that is derived from a genetically modified strain of *Geobacillus stearothermophilus*." Arnold Decl. ¶59. *Geobacillus stearothermophilus* is a newly accepted name for *Bacillus stearothermophilus*. The '031 patent and its claims use the old name. *Id.*, ¶60.

Genencor's Spezyme Ethyl alpha-amylase enzyme is a protein of 484 amino acids. *See* Christian Jørgensen Decl. ¶45.[7] Using the amino acid sequence of SEQ ID NO:3 of the '031

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[6] *Bacillus stearothermophilus* is the name of a naturally-occurring bacteria species in which alpha-amylase is produced.

[7] "Christian Jørgensen Decl." refers to the Declaration of Christian Isak Jørgensen, Ph.D., dated June 16, 2005, submitted with this memorandum as Exh. F.

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patent for numbering purposes, the amino acids at positions 179 and 180 of the Genencor alpha-amylase protein have been deleted. Devereux Decl. ¶41; Arnold Decl. ¶¶67 and 83. Further, the Spezyme Ethyl alpha-amylase protein has an amino acid sequence which exhibits "at least 95% homology," both to the amino acid sequence of the parent *Bacillus stearothermophilus* alpha-amylase, and to the sequence of SEQ ID NO:3. Arnold Decl. ¶¶70 and 74; Devereux Decl. ¶¶41-42. An alignment of the Spezyme Ethyl alpha-amylase's amino acid sequence with the amino acid sequence of its parent shows that all of the aligning amino acid residues are identical in these two proteins. Devereux Decl. ¶36; Arnold Decl. ¶66.

IV. ARGUMENT: NOVOZYMES' MOTION FOR INJUNCTIVE RELIEF SHOULD BE GRANTED

A party is entitled to a preliminary injunction against continued patent infringement when it establishes: (1) a reasonable likelihood of success on the merits of its case; (2) irreparable harm if it is not granted an injunction; (3) a balance of hardships tipping in its favor; and (4) the injunction's non-adverse impact on the public interest. *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1363 (Fed. Cir. 2001); *Reebok Int'l Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1555 (Fed. Cir. 1994) (cited in *eSpeed, Inc. v. Brokertec USA, L.L.C.*, 2004 U.S. Dist. LEXIS 385, *7, 69 U.S.P.Q.2d 1466, 1468 (D. Del. Jan. 14, 2004) (Jordan, J.)); *Illinois Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d 679, 681 (Fed. Cir. 1990); *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1451 (Fed. Cir. 1988). When deciding whether a preliminary injunction should be granted or denied, the court should weigh and measure each of these four factors against the other factors, and against the magnitude of the relief requested. *eSpeed*, 2004 U.S. Dist. LEXIS 385, at *7, 69 U.S.P.Q.2d at 1469 (citing *Hybritech*, 849 F.2d at 1451 n.12)). Here, consideration of these factors demonstrates that Novozymes is entitled to a preliminary

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injunction against the manufacture, use, offer for sale, sale, or importation, of Genencor's infringing Spezyme Ethyl alpha-amylase product.

A. NOVOZYMES IS LIKELY TO SUCCEED ON THE MERITS OF ITS CASE

To satisfy the requirement that it is reasonably likely to succeed in its case, Novozymes must show that, "in light of the presumptions and burdens that will inhere at trial on the merits," (1) the defendants likely infringe the '031 patent, and (2) the asserted claims of the '031 patent will likely withstand the defendants' challenges to validity. *The Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367. 2005 U.S. App. LEXIS 7405, at *7 (Fed. Cir. Apr. 29, 2005); *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001), (cited in *eSpeed*, 2004 U.S. Dist. LEXIS 385, at *12, 69 U.S.P.Q.2d 1470). The determination of patent infringement is a two-step process. First, the meaning and scope of the patent claim(s) are construed. Second, the structure or process under consideration is compared with the claim as properly construed. *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 796 (Fed. Cir. 1990); *see also Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996).

1. Construction of '031 Patent Claims 1 and 3

Claim construction is a threshold inquiry in any assessment of infringement. *Athletic Alternatives v. Prince Mfg.*, 73 F.3d 1573, 1578 (Fed. Cir. 1996) (citing *Markman*, 52 F.3d at 976). Claim construction is a question of law, exclusively within the province of the court. *Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1455 (Fed. Cir. 1998) (*en banc*); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). A proper claim construction must give meaning to every claim limitation. *Harris Corp. v. IXYS Corp.*, 114 F.3d 1149, 1152 (Fed. Cir.

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1997). When construing a patent claim, one should look first to the intrinsic evidence of record, *i.e.*, the patent itself, including the claims, the specification, the prosecution history before the U.S. Patent and Trademark Office ("PTO"), and the cited prior art. *CVI/Beta Ventures v. Tura LP*, 112 F.3d 1146, 1152 (Fed. Cir. 1997).

Claim construction begins most fundamentally with the language of the claims. *Johnson Worldwide Assocs. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed. Cir. 1999); *Bell Communications Research v. Vitalink Communications Corp.*, 55 F.3d 615, 619-620 (Fed. Cir. 1995). The words of a claim are given their ordinary meaning to one skilled in the art, unless it appears from the patent and prosecution history that the words were used differently by the inventors. *Vitronics*, 90 F.3d at 1582. "Common words, unless the context suggests otherwise, should be interpreted according to their ordinary meaning." *Desper Products, Inc. v. QSound Labs, Inc.*, 157 F.3d 1325, 1336 (Fed. Cir. 1998). However, "[t]he specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Vitronics*, 90 F.3d at 1582. When the specification acts as a dictionary, expressly defining a term used in the claims, it is "the single best guide to the meaning of a disputed term." *Id.* Depending upon the particular circumstances, relevant dictionaries and technical encyclopedias from the time period that the applicable patent application was filed in the PTO may be consulted to determine the ordinary meaning of such terms, as long as their definitions are read and applied consistently with the context of the applicable terms as used in the patent specification. *See, e.g., Texas Digital Sys., Inc. v. Telegenix, Inc*, 308 F.3d 1193, 1202-03 (Fed. Cir. 2002).

a. Claim 1 of the '031 Patent

Claim 1 of the '031 patent reads as follows:

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> A **variant of a parent *Bacillus stearothermophilus* alpha-amylase**, wherein the variant has an amino acid sequence which has **at least 95% homology** to the parent *Bacillus stearothermophilus* alpha-amylase and **comprises a deletion of amino acids 179 and 180**, using SEQ ID NO:3 for numbering, and wherein the variant has **alpha-amylase activity**.[8]

Here, the intrinsic evidence is sufficient for construing the claim terms, as claim 1 is unambiguous and clear. The '031 patent specification defines several terms recited in claim 1. The remaining terms should be given their ordinary meanings.

"Variant of a parent *Bacillus stearothermophilus* alpha-amylase"

The preamble, *i.e.*, introduction portion, of claim 1 recites "[a] variant of a parent *Bacillus stearothermophilus* alpha-amylase." Ordinarily, a claim preamble that simply states a purpose or intended use of a claimed composition is not a positive claim limitation. However in this instance, the preamble is necessary to give "life and meaning" to the claim and, therefore, is a positive claim limitation. *See Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989) ("[The] preamble in this instance does not merely state a purpose or intended use for the claimed structure ... Rather, those words do give 'life and meaning' and provide further positive limitations to the invention claimed").

Here, the preamble specifies the particular type of enzyme claimed: an "alpha-amylase," which is an enzyme that catalyzes the breakdown (or "hydrolysis") of certain chemical bonds in starch. *See* Arnold Decl. ¶39.

The preamble term "*Bacillus stearothermophilus*" refers to a particular species of bacteria. Arnold Decl. ¶39. As also explained above, the accepted name for *Bacillus*

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[8] The above terms in **bold** from claim 3 are discussed in detail herein.

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stearothermophilus is now *Geobacillus stearothermophilus*. Arnold Decl. ¶40, n.4. A "*Bacillus stearothermophilus* alpha-amylase" is the enzyme produced by an alpha-amylase gene isolated from *Bacillus stearothermophilus*, a.k.a. *Geobacillus stearothermophilus*. Arnold Decl. ¶40.

The preamble of claim 1 refers to both a "parent" *Bacillus stearothermophilus* alpha-amylase, and a "variant" thereof. These terms have their ordinary meaning in the art. A "variant" protein is a protein that has been modified to have one or more changes in its amino acid sequence when compared to a "parent" protein.[9] Arnold Decl. ¶41. The amino acid sequence of a "variant" protein can differ from that of the "parent" protein by the addition, deletion, or substitution of one or more amino acids in its sequence. Arnold Decl. ¶41; *see also* ¶35. A "parent" protein is a protein having an amino acid sequence without the modification that results in a variant.[10] *Id.* ¶35. Thus, a "parent *Bacillus stearothermophilus* alpha-amylase" is a protein having alpha-amylase activity that is encoded by a gene from *Bacillus stearothermophilus*. *Id.* ¶40. The amino acid sequence of a "variant" alpha-amylase is different from that of a corresponding "parent," in that it will have one or more amino acid substitutions, deletions, or additions. *Id.* ¶41.

Accordingly, the preamble of claim 1 should be construed to mean a "variant" alpha-amylase enzyme (*i.e.*, an enzyme that breaks down certain chemical bonds in starch) that can be derived from a "parent" alpha-amylase of the bacterial species *Bacillus (Geobacillus) stearothermophilus*. However, the claimed variant alpha-amylase has a different amino acid

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[9] This definition is consistent with the dictionary definition of "variant": "one of two or more…things exhibiting usu. slight differences…" Webster's Ninth New Collegiate Dictionary (1991), p. 1304 (Exh. E).

[10] This meaning is also consistent with the dictionary definition of "parent": "the material or source from which something is derived." Exh. E, p. 855.

sequence (*i.e.*, one or more substitutions, insertions, or deletions) when compared to the "parent" alpha-amylase from *Bacillus stearothermophilus*. Arnold Decl. ¶42.

"At least 95% homology"

Normally, the similarity between amino acid sequences of proteins is assessed by calculating their "percent identity." Devereux Decl. ¶12; Arnold Decl. ¶27. The '031 patent discusses the "percent homology" of amino acid sequences and defines that term to mean the same thing as "percent identity." Arnold Decl. ¶¶27, and 43-44. *See, also,* Devereux Decl. ¶13. Specifically, the '031 patent describes comparing amino acid sequences as follows:

> An amino acid sequence is considered to be X% homologous to the parent [alpha]-amylase if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in *Science* 227 (1985) p. 1435, reveals an identity of X%. The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used, employing default values for GAP penalties [Genetic Computer Group (1991) Programme Manual for the GCG Package, version 7, 575 Science Drive, Madison, Wis. USA 53711].

Exh. A at 4:36-45; *see also* Arnold Decl. ¶44.

Thus, the claim limitation "wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase" should be construed as requiring that the amino acid sequence of the variant is at least 95% identical when compared to the amino acid sequence of the corresponding parent *Bacillus stearothermophilus* alpha-amylase, using an algorithm such as that included with the GAP program. Arnold Decl. ¶45.

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"Comprises a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering"

The transition term "comprises" in a patent claim is open-ended and means that the claim does not exclude additional, unrecited components such as, for example in this case, other amino acid deletions, substitutions, or additions. *A.K. Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2004); *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1178 (Fed. Cir. 1991); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1271 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987). The deletion of an amino acid residue in a variant protein refers to the absence or removal of that amino acid residue, through mutation or modification of DNA for a parent protein. Arnold Decl. ¶46. To determine whether the specified amino acids of this claim limitation are deleted, the sequence is aligned and compared with a corresponding reference sequence (in this instance, SEQ ID NO:3). Arnold Decl. ¶¶21-24. Hence, the claimed variant alpha-amylase sequence, when aligned with SEQ ID NO:3 (*e.g.*, using the GAP computer program), should have "gaps" or deletions at positions aligning with amino acids 179 and 180 of the '031 parent. Arnold Decl. ¶47. *See also Id.*, ¶¶23-24. However, the claimed variant may also contain additional amino acid substitutions, insertions or deletions. *Id.*, ¶48.

"The variant has alpha-amylase activity"

Alpha-amylase enzymes are characterized by having a particular catalytic activity, as explained above. Particularly, these enzymes catalyze the hydrolysis (*i.e.*, the break-down) of certain chemical bonds (*i.e.*, alpha-1,4-glucosidic bonds) in starch. Arnold Decl. ¶49.

* * * *

Claim 1 of the '031 patent therefore claims a "variant" with a different amino acid sequence (*i.e.*, having one or more substitutions, insertions or deletions) from a "parent" alpha-

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amylase (*i.e.*, an enzyme that breaks down certain chemical bonds in starch) of the bacteria species *Bacillus (Geobacillus) stearothermophilus*. When aligned with the parent alpha-amylase's amino acid sequence using an algorithm such as GAP, the variant's amino acid sequence is more than 95% identical to the parent's. However, the variant's amino acid sequence differs from the parent by *at least* the deletion of amino acids at positions aligning with amino acids 179 and 180 of SEQ ID NO:3. The claimed variant also has the activity of an alpha-amylase enzyme – *i.e.*, the variant has the ability to break down the alpha-1,4-glucosidic bonds in starch. Arnold Decl. ¶50.

b. Claim 3 of the '031 Patent

Claim 3 of the '031 patent (Exh. A at 65:10-17) reads as follows:

> A **variant alpha-amylase**, wherein the variant has **at least 95% homology** to SEQ ID NO:3 and **comprises a deletion of amino acids 179 and 180**, using SEQ ID NO:3 for numbering and wherein the variant has **alpha-amylase activity**.

Here, the intrinsic evidence is likewise sufficient for construing the claim terms since claim 3 is unambiguous and clear. Several of the terms in claim 3 are also found in claim 1. Accordingly, these terms must be given the same construction. *See, e.g., Southwall Techs. v. Cardinal IG Co.*, 54 F.3d 1570, 1579 (Fed. Cir. 1995) (a claim term "cannot be interpreted differently in different claims"). In this section of the memorandum, each limitation of claim 3 will be considered.

"A variant alpha-amylase"

The preamble of claim 3 recites "[a] variant alpha-amylase." The terms "variant" and "alpha-amylase" in the preamble are claim limitations as in claim 1, discussed above, and must be given the same construction in '031 claim 3. Arnold Decl. ¶52.

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"Wherein the variant has at least 95% homology to SEQ ID NO:3"

The term "at least 95% homology" is construed above with respect to claim 1, and has the same meaning here. Thus, the claim limitation "wherein the variant has at least 95% homology to SEQ ID NO:3" should be construed as requiring the amino acid sequence of the variant to be compared to the amino acid sequence of SEQ ID NO:3 using an algorithm, such as that included with the GAP program mentioned in the patent. Exh. A at 65:45-49; Arnold Decl. ¶53.

"Comprises a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering"

This limitation should be construed in the same manner as discussed above concerning the same limitation in '031 claim 1. Arnold Decl. ¶54-55.

"The variant has alpha-amylase activity"

Similarly, this limitation should be construed in the same manner as discussed above concerning the same limitation in '031 claim 1. Arnold Decl. ¶56.

* * * *

In summary, therefore, claim 3 of the '031 patent should be construed as being directed to a "variant" alpha-amylase enzyme. When aligned with SEQ ID NO:3 for the '031 patent, the sequence of the claimed variant is 95% or more identical to SEQ ID NO:3. At the same time, however, the claimed variant's amino acid sequence differs from SEQ ID NO:3 *at least* by a deletion of amino acids aligning at positions 179 and 180 of SEQ ID NO:3 (and may also contain additional amino acid substitutions, insertions and/or deletions). The claimed variant also has

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the activity of an alpha-amylase enzyme – *i.e.*, it can break down the alpha-1,4-glucosidic bonds in starch. Arnold Decl. ¶50.

2. Genencor's Alpha-amylase Product Infringes '031 Claims 1 and 3

The alpha-amylase enzyme in Genencor's Spezyme Ethyl product satisfies each and every limitation of '031 claims 1 and 3. Therefore, literal infringement is present. *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279 1282 (Fed. Cir. 1986) (literal infringement exists where the accused product embodies every limitation of a patent claim).

Novozymes has obtained samples of Genencor's Spezyme Ethyl alpha-amylase product and has analyzed them in the manner described below to determine its amino acid sequence.[11] Novozyme has also identified a parent alpha-amylase that is encoded by an alpha-amylase gene from the natural *Bacillus stearothermophilus* isolate ATCC 31,195.[12] Christian Jørgensen Decl. ¶7. The sequence of both this gene and the amino acid sequence it encodes are publicly available from GeneBank, a comprehensive public database of genetic and amino acid sequences. Christian Jørgensen Decl. ¶8. Novozymes has obtained and analyzed the parent alpha-amylase expressed by this gene. *See* Christian Jørgensen Decl. ¶¶7-9 and 35-45. The analysis shows clearly that Genencor's Spezyme Ethyl product contains a variant of the *Bacillus (Geobacillus) stearothermophilus* ATCC 31,195 isolate parent alpha-amylase. Arnold Decl.

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[11] Novozymes' analysis of the Spezyme Ethyl samples is described in the Declaration of Steen Troels Jørgensen, dated May 19, 2005 and in the Declaration of Christian Isak Jørgensen, dated June 16, 2005 (the "Christian Jørgensen Decl."), both of which are submitted with this memorandum as Exhs. F and G, respectively.

[12] The "ATCC 31,195 isolate" is so named because it has been deposited with, and is available from, a repository of microorganisms called the American Type Culture Collection or "ATCC." ATCC 31,195 refers to the "accession number" that the ATCC uses to identify that particular microorganism deposit. Arnold Decl. no. 5.

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¶67. Moreover, when aligned with the amino acid sequence of that parent alpha-amylase, Spezyme Ethyl's amino acid sequence has at least 95% "homology," *i.e.*, is 95% identical, thereto. Arnold Decl. ¶70. The Spezyme Ethyl alpha-amylase also has more than "95% homology," *i.e.*, is more than 95% identical to '031 patent SEQ ID NO:3 (*Id.* ¶74), and has a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering purposes. *Id.*, ¶83. The analysis demonstrates further that the variant alpha-amylase in Spezyme® Ethyl also has alpha-amylase activity. Arnold Decl. ¶85. Literal infringement is, therefore, clear.

a. Infringement of Claim 1

i. Spezyme Ethyl Contains a Variant of a Parent *Bacillus stearothermophilus* Alpha-amylase

Claim 1 recites and is directed to "[a] variant of a parent *Bacillus stearothermophilus* alpha-amylase." Genencor itself has asserted that its "SPEZYME® ETHYL enzyme contains a thermostable starch-hydrolyzing [alpha]-amylase ... that is derived from a genetically modified strain of *Geobacillus stearothermophilus*." Arnold Decl. ¶59. The Spezyme Ethyl alpha-amylase variant differs from a parent *Bacillus stearothermophilus* ATCC strain 31,195 by the deletion of residues 179 and 180. *Id.* ¶66. Clearly, Genencor's Spezyme Ethyl product contains an enzyme that is a "variant of a parent *Bacillus stearothermophilus* alpha-amylase." *Id.* ¶¶67 and 87. The Spezyme Ethyl alpha-amylase can be readily obtained by deleting amino acid residues 179 and 180 of that parent. *Id.*, ¶67.

ii. Spezyme Ethyl Has At Least 95% Homology to the Parent *Bacillus stearothermophilus* Alpha-amylase

Claim 1 also specifies that "the variant has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase." The "homology," *i.e.*, percent identity, between the amino

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acid sequence for Genencor's Spezyme® Ethyl obtained by Novozymes, and the amino acid sequence of its corresponding parent *Bacillus stearothermophilus* alpha-amylase, was determined to be 100%. Jørgensen Decl. ¶36; Arnold Decl. ¶69. Hence, the variant alpha-amylase in Genencor's Spezyme Ethyl product has at least "95% homology" to the parent *Bacillus stearothermophilus* alpha-amylase. Arnold Decl. ¶¶70 and 88.

Indeed, Spezyme® Ethyl differs from the parent ATCC 31,195 alpha-amylase *only* by the deletion of amino acids 179 and 180, and by missing just three amino acids from one end (called the "C-terminus") of the parent ATCC 31,195 alpha-amylase. Devereux Decl. ¶40; Arnold Decl. ¶66. Apart from these, the two sequences are *entirely* identical. Devereux Decl. ¶40; *see also* Arnold Decl. ¶66.

The very high level of similarity between these amino acid sequences is apparent from visual inspection of the following table, which shows the aligned amino acid sequences for Genencor's Spezyme® Ethyl and parent *Bacillus stearothermophilus* alpha-amylase (ATCC strain 31,195), SEQ ID NO:3, and the sequence from Fig. 1 of the '031 patent (Exh. A).[13] Differences between these amino acid sequences are highlighted, so that they can be more easily seen. Deletions of amino acids (at positions 179 and 180) are shown as "*". The two amino acids shown at the end of the amino acid sequence (called the "C-terminus" of the sequence) of the parent alpha-amylase (and not found in the Spezyme® Ethyl sequence), are ignored for purposes of assessing homology, according to the algorithms specified by the '031 patent. *See* Devereux Decl. ¶12 and ¶25, n. 5. Thus, using the GAP computer program in the patent

[13] This alignment is also discussed in the Devereux Decl. (¶¶37-50) and in the Arnold Decl. (¶¶81-82).

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specification (Exh. A at 4:36-45), the homology between the two sequences is 100%. Devereux Decl. ¶¶36 and 40; Arnold Decl. ¶¶69-70.

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Alpha-Amylase Alignments

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Spezyme       AAPFNGTMMQ YFEWYLPDDG TLWTKVANEA NNLSSLGITA LWLPPAYKGT   50
SEQ ID NO:3   AAPFNGTMMQ YFEWYLPDDG TLWTKVANEA NNLSSLGITA LWLPPAYKGT   50
Figure 1      AAPFNGTMMQ YFEWYLPDDG TLWTKVANEA NNLSSLGITA LWLPPAYKGT   50
ATCC 31,195   AAPFNGTMMQ YFEWYLPDDG TLWTKVANEA NNLSSLGITA LWLPPAYKGT   50

Spezyme       SRSDVGYGVY DLYDLGEFNQ KGTVRTKYGT KAQYLQAIQA AHAAGMQVYA  100
SEQ ID NO:3   SRSDVGYGVY DLYDLGEFNQ KGAVRTKYGT KAQYLQAIQA AHAAGMQVYA  100
Figure 1      SRSDVGYGVY DLYDLGEFNQ KGTVRTKYGT KAQYLQAIQA AHAAGMQVYA  100
ATCC 31,195   SRSDVGYGVY DLYDLGEFNQ KGTVRTKYGT KAQYLQAIQA AHAAGMQVYA  100

Spezyme       DVVFDHKGGA DGTEWVDAVE VNPSDRNQEI SGTYQIQAWT KFDFPGRGNT  150
SEQ ID NO:3   DVVFDHKGGA DGTEWVDAVE VNPSDRNQEI SGTYQIQAWT KFDFPGRGNT  150
Figure 1      DVVFDHKGGA DGTEWVDAVE VNPSDRNQEI SGTYQIQAWT KFDFPGRGNT  150
ATCC 31,195   DVVFDHKGGA DGTEWVDAVE VNPSDRNQEI SGTYQIQAWT KFDFPGRGNT  150

Spezyme       YSSFKWRWYH FDGVDWDESR KLSRIYKF** IGKAWDWEVD TENGNYDYLM  198
SEQ ID NO:3   YSSFKWRWYH FDGVDWDESR KLSRIYKFRG IGKAWDWEVD TENGNYDYLM  200
Figure 1      YSSFKWRWYH FDGVDWDESR KLSRIYKFRG IGKAWDWEVD TENGNYDYLM  200
ATCC 31,195   YSSFKWRWYH FDGVDWDESR KLSRIYKFRG IGKAWDWEVD TENGNYDYLM  200

Spezyme       YADLDMDHPE VVTELKNWGK WYVNTTNIDG FRLDAVKHIK FSFFPDWLSY  248
SEQ ID NO:3   YADLDMDHPE VVTELKSWGK WYVNTTNIDG FRLDAVKHIK FSFFPDWLSD  250
Figure 1      YADLDMDHPE VVTELKNWGK WYVNTTNIDG FRLDAVKHIK FSFFPDWLSY  250
ATCC 31,195   YADLDMDHPE VVTELKNWGK WYVNTTNIDG FRLDAVKHIK FSFFPDWLSY  250

Spezyme       VRSQTGKPLF TVGEYWSYDI NKLHNYITKT NGTMSLFDAP LHNKFYTASK  298
SEQ ID NO:3   VRSQTGKPLF TVGEYWSYDI NKLHNYIMKT NGTMSLFDAP LHNKFYTASK  300
Figure 1      VRSQTGKPLF TVGEYWSYDI NKLHNYITKT DGTMSLFDAP LHNKFYTASK  300
ATCC 31,195   VRSQTGKPLF TVGEYWSYDI NKLHNYITKT NGTMSLFDAP LHNKFYTASK  300

Spezyme       SGGAFDMRTL MTNTLMKDQP TLAVTFVDNH DTEPGQALQS WVDPWFKPLA  348
SEQ ID NO:3   SGGTFDMRTL MTNTLMKDQP TLAVTFVDNH DTEPGQALQS WVDPWFKPLA  350
Figure 1      SGGAFDMRTL MTNTLMKDQP TLAVTFVDNH DTEPGQALQS WVDPWFKPLA  350
ATCC 31,195   SGGAFDMRTL MTNTLMKDQP TLAVTFVDNH DTEPGQALQS WVDPWFKPLA  350
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Spezyme	YAFILTRQEG YPCVFYGDYY GIPQYNIPSL KSKIDPLLIA RRDYAYGTQH	398
SEQ ID NO:3	YAFILTRQEG YPCVFYGDYY GIPQYNIPSL KSKIDPLLIA RRDYAYGTQH	400
Figure 1	YAFILTRQEG YPCVFYGDYY GIPQYNIPSL KSKIDPLLIA RRDYAYGTQH	400
ATCC 31,195	YAFILTRQEG YPCVFYGDYY GIPQYNIPSL KSKIDPLLIA RRDYAYGTQH	400
Spezyme	DYLDHSDIIG WTREGVTEKP GSGLAALITD GPGGSKWMYV GKQHAGKVFY	448
SEQ ID NO:3	DYLDHSDIIG WTREGVTEKP GSGLAALITD GPGGSKWMYV GKQHAGKVFY	450
Figure 1	DYLDHSDIIG WTREGGTEKP GSGLAALITD GPGGSKWMYV GKQHAGKVFY	450
ATCC 31,195	DYLDHSDIIG WTREGVTEKP GSGLAALITD GPGGSKWMYV GKQHAGKVFY	450
Spezyme	DLTGNRSDTV TINSDGWGEF KVNGGSVSVW VPRKTT	484
SEQ ID NO:3	DLTGNRSDTV TINSDGWGEF KVNGGSVSVW VPRKTTVSTI AWSITTRPWT	500
Figure 1	DLTGNRSDTV TINSDGWGEF KVNGGSVSVW VPRKTTVSTI ARPITTRPWT	500
ATCC 31,195	DLTGNRSDTV TINSDGWGEF KVNGGSVSVW VPRKTTVST	489
Spezyme		
SEQ ID NO:3	DEFVRWTEPR LVAW	514
Figure 1	GEFVRWTEPR LVAW	514
ATCC 31,195		

iii. The Amino Acids Corresponding to Positions 179 and 180 in SEQ ID NO:3 Are Deleted in Spezyme Ethyl

Claim 1 specifies that the alpha-amylase variant contains "a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering." As shown in the above table, the amino acid sequence of Spezyme Ethyl's variant alpha-amylase has a deletion of two amino acid residues, 179 and 180 (Arginine and Glycine, respectively), from the sequence of the parent SEQ ID NO:3. Arnold Decl. ¶¶80-83. *See also* Devereux Decl. ¶¶38 and 41.

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iv. Spezyme Ethyl Has Alpha-amylase Activity

Claim 1 specifies additionally that "the variant has alpha-amylase activity." Genencor sells its Spezyme Ethyl alpha-amylase product as an alpha-amylase, and specifically asserts that its product has alpha-amylase activity:

> The endo-amylase [*i.e.*, alpha-amylase] in SPEZYME® ETHYL enzyme randomly hydrolyzes alpha-1,4-glucosidic bonds to quickly reduce the viscosity of gelatinized starch or grain mash, producing soluble dextrins and saccharides under a variety of conditions.

Arnold Decl. ¶84. Clearly, the alpha-amylase enzyme in Genencor's Spezyme Ethyl product also has alpha-amylase activity; it "hydrolyzes" or "cleaves," *i.e.*, cuts off or breaks, alpha-1,4-glucosidic chemical bonds in starch. Arnold Decl. ¶85; *see also Id.*, ¶90.

* * * *

In summary, the Spezyme Ethyl product satisfies each and every limitation of '031 patent claim 1. Arnold Decl. ¶91. Literal infringement of '031 claim 1 is clear.

b. Infringement of Claim 3

i. Spezyme Ethyl Contains a Variant Alpha-amylase

Claim 3 recites and is directed to "[a] variant alpha-amylase," and Novozymes' analysis clearly shows that the Spezyme Ethyl product contains a "variant alpha-amylase." Arnold Decl. ¶¶59-67 and ¶92. Genencor has also asserted this fact. *See Id.* ¶59.

ii. Spezyme Ethyl Has At Least 95% Homology to SEQ ID NO:3

Claim 3 specifies that "the variant has at least 95% homology to SEQ ID NO:3." The homology of the amino acid sequence for Genencor's Spezyme Ethyl enzyme to SEQ ID NO:3

was determined to be greater than 98%. Hence, the variant alpha-amylase in Genencor's Spezyme Ethyl product has at least 95% homology to SEQ ID NO:3. Arnold Decl. ¶¶71-74 and ¶93; *see also* Devereux Decl. ¶25.

The high level of similarity between these amino acid sequences is apparent from their alignment in the above Table. *See also* Devereux Decl. ¶39. Only five out of the 484 amino acids differ in the alignment of SEQ ID NO:3 and Spezyme® Ethyl.[14] The remaining 27 amino acids shown at the C-terminal end of SEQ ID NO:3 (which are not found in the Spezyme® Ethyl sequence), are ignored for purposes of assessing "homology" (*i.e.*, percent identity) according to the algorithms specified by the '031 patent. Devereaux Decl. ¶25 n.5. Thus, using the GAP computer program as stated in the patent specification (4:36-45), the homology between the two sequences is greater than 98%. *Id.*

iii. The Amino Acids Corresponding to Positions 179 and 180 in SEQ ID NO:3 Are Deleted in Spezyme Ethyl

Claim 3 specifies that the alpha-amylase variant contains "a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering." As shown in the table above, the amino acid sequence of Spezyme Ethyl's variant alpha-amylase has a deletion of two amino acids, 179 and 180 (Arginine and Glycine, respectively), from the sequence of SEQ ID NO:3. Arnold Decl. ¶¶80-83 and ¶94. *See also* Devereux Decl. ¶38.

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[14] The residues in SEQ ID No:3 that are different from their corresponding residue in Spezyme® Ethyl (A73, S217, D250, M278, and T304) are highlighted in the above Table.

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iv. Spezyme Ethyl Has Alpha-Amylase Activity

As discussed above regarding claim 1, there is no question that Genencor's alpha-amylase product has the activity of an alpha-amylase. *See* Arnold Decl. ¶¶84-85 and ¶94.

* * * *

In summary, therefore, each of the limitations of '031 claim 3 is satisfied by the Spezyme Ethyl alpha-amylase. Arnold Decl. ¶96. Literal infringement is clear.

c. The '031 Patent Is Valid and Enforceable

An issued patent is presumed valid. 35 U.S.C. § 282. This statutory presumption of validity exists at every stage of a litigation -- including the preliminary injunction stage. *H.H. Robertson v. United Steel Deck, Inc.*, 820 F.2d 384, 385 (Fed. Cir. 1987) (a preliminary injunction is determined "in the context of the presumptions and burdens that would inhere at trial on the merits"); *see also Canon Computer Sys., Inc. v. Nu-Kote Int'l, Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998). Accordingly, the heavy burden of showing invalidity rests squarely and "immutabl[y]" on defendants. *H.H. Robertson*, 820 F.2d at 388; *CVI / Beta Ventures*, 893 F. Supp. at 516 ("Only if the Court finds that Defendants have raised a substantial question [emphasis added] in support of invalidity do Plaintiffs need to consider the presentation of further evidence."); *see also eSpeed*, 2004 U.S. Dist. LEXIS 385, at *12-13, 69 U.S.P.Q.2d at 1470.

In its Answer, Genencor made only general assertions that the '031 patent is invalid ("35 U.S.C. §§ 101, 102, 103 and/or 112"). Genencor gave no reasons for its boilerplate allegations. While Genencor did provide a bit more regarding its allegations of unenforceability -- allegations which must be pled "with particularity" -- these allegations are likewise unfounded and, at a

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minimum, do not raise a substantial question of unenforceability. *Cf. eSpeed*, 2004 U.S. Dist. LEXIS 385 at *12, 69 U.S.P.Q.2d at 1470. Genencor has alleged that the '031 patent is unenforceable due to acts of inequitable conduct on the part of various Novozymes personnel. These allegations exemplify the Federal Circuit's oft-cited, disapproving observation made more than 17 years ago -- and which is just as valid today -- that the "habit of charging inequitable conduct in almost every major patent case has become an absolute plague." *Burlington Indus., Inc. v. Dayco, Inc.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988), (cited in *Molins PLC v. Textron*, 48 F.3d 1172, 1182 (Fed. Cir. 1995), *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 n.15 (Fed. Cir. 1988), and *ISCO Int'l, Inc. v. Conductus, Inc.*, 279 F. Supp.2d 489, 505-06 (D. Del. 2003)).

Genencor focuses on a declaration by Borchert ("the Declaration") submitted by Novozymes during USPTO prosecution of the '031 patent. The Declaration compares the activity of a variant enzyme of the '031 patent with a variant enzyme of a prior art reference and presents the results of experiments conducted or supervised by one of the inventors of the '031 patent. Borchert Decl. ¶¶3-6.[15] The experiments demonstrate that a variant enzyme of the '031 patent (having the two amino acids deleted at *positions 179 and 180*) exhibited a 63-fold improvement in half-life at elevated temperatures, compared to the parent enzyme without the deletion. The prior art enzyme (having two amino acids deleted at *positions 176 and 177*) exhibited only an 11-fold improvement in half-life under the same conditions. The Declaration concludes that the deletion of the '031 patent variant provides a relative improvement in thermal stability, that is 5 to 6 times higher than that seen in the prior art variant. The Declaration

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[15] "Borchert Decl." refers to the "Declaration of Torben A. Borchert Under 37 C.F.R. 1.132" from the '031 patent's prosecution history (Exh. H).

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includes a statistical analysis confirming that the results are statistically significant, and opines that the results are "very surprising as the effect of the double deletion in BSG [the inventive variant] is significantly greater than what would have been expected based on the combined teachings of [the prior art]." *Id.* at ¶9.

The Borchert Declaration included all of the relevant experimental details and statistical analysis for the USPTO Examiner to consider for herself in assessing the probative value of the Declaration. Upon her consideration of the Declaration, its experiment details, and its statistical analysis, the Examiner concluded that the Declaration "establishes that the claimed variants exhibit unexpectedly large increases in thermostability when compared to the increases in thermostability obtained for the corresponding mutations taught by [the prior art]. " Notice of Allowability" from the '013 patent's prosecution history (Exh. I).

Genencor has not set forth with any particularity how submission of the Declaration constitutes intentional, purposeful, material misrepresentations of material facts, amounting to any evidence, let alone clear and convincing evidence, of inequitable conduct before the USPTO. *See, e.g., Ferguson Beauregard Logic Controls, Division of Dover Resources, Inc. v. Mega Sys., LLC.*, 350 F.3d 1327, 1344 (Fed. Cir. 2003) (inequitable conduct must be pled with particularity); *see also EMC Corp. v. Storage Tech. Corp.*, 921 F. Supp. 1261, 1263 (D. Del. 1996 ("particularity requirement of Rule 9(b) applies to inequitable conduct charges"). Accordingly, no substantial question of unenforceability has been raised by Genencor to diminish the likelihood of success by Novozymes on the merits.

* * * *

In summary regarding the "reasonable likelihood of success" preliminary injunction factor, Novozymes has made a clear showing that the '031 patent is infringed by Genencor.

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There is no evidence to conclude that the '031 patent is invalid or unenforceable. Therefore, this factor weighs clearly in Plaintiff's favor.

B. NOVOZYMES WILL BE IRREPARABLY HARMED IF AN INJUNCTION DOES NOT ISSUE

A patentee is entitled to a presumption of irreparable harm by making a "clear showing" of a likelihood of success on the merits. *Oakley, Inc. v. Sunglass Hut Int'l,* 316 F.3d 1331, 1345 (Fed. Cir. 2003) (finding that even where the question of validity and infringement was "close," patentee was entitled to a presumption of irreparable harm); *see also John Mezzalingua Assoc., Inc. v. Arris Int'l, Inc.* 298 F. Supp. 2d 813, 821 (W.D. Wisc. 2003) (following Federal Circuit's *Oakley* decision, and finding patentee entitled to presumption of irreparable harm because "[a] 'clear showing' does not have to be a slam dunk showing"); *Amazon.com*, 239 F.3d at 1350 ("Irreparable harm is presumed when a clear showing of patent validity and infringement has been made."); *Impax Lab., Inc. v. Aventis Pharms., Inc.*, 235 F. Supp. 2d 390, 395-96 (D. Del. 2002) ("Irreparable harm is presumed when a clear showing of patent validity and infringement has been made" and granting preliminary injunction in patent case) (citing *Amazon.com*, 239 F.3d at 1350). "This presumption derives in part from the finite term of the patent grant, for patent expiration is not suspended during litigation, and the passage of time can work irremediable harm." *Bell & Howell Document Mgmt. Prods. v. Altek Sys.*, 132 F.3d 701, 708 (Fed. Cir. 1997) (quoting *H.H. Robertson*, 820 F.2d at 390, *overruled on other grounds, Markman,* 52 F.3d at 977); *Impax Lab.*, 235 F. Supp. 2d at 395-96 (quoting *Bell & Howell*, and granting preliminary injunction in patent case).

Novozymes is entitled to the presumption of irreparable harm because, as demonstrated above, it has made a clear showing that it will succeed on the merits of its case. But, even if

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Novozymes were not entitled to the presumption (which it is so entitled), there is other and substantial evidence that, absent immediate injunctive relief to return to the *status quo*, Novozymes will suffer irreparable harm. In particular, the unabated marketing and sales of Genencor's infringing *alpha-amylase* enzyme product have already caused, and will likely continue to cause, (i) irreversible alteration of relevant market conditions to the significant detriment of Novozymes; (ii) Novozymes' significant loss of [redacted], goodwill, and customers, as well as the loss of its related convoyed sales of *gluco-amylase* enzyme products; and (iii) Novozymes' loss of a large annual supply agreement, expected to be awarded in just four months from now (in October 2005), covering a collective of domestic plants [redacted], that will not reopen until October 2006. None of these losses, and certainly not the cumulative effect of the losses, can be adequately compensated by money damages. LeFebvre Decl. ¶6.

1. Genencor's Infringement Will Irreversibly Alter Market Conditions Which Cannot Be Remedied By An Award of Money Damages

Irreparable harm is readily established when an infringer, by entering the marketplace, alters market conditions so that the conditions are unable to return to their pre-infringement state. In *Polymer Techs., Inc. v. Bridwell,* 103 F.3d 970 (Fed. Cir. 1996), the Federal Circuit stated the following in this regard:

> Competitors change the marketplace. Years after infringement has begun, it may be impossible to restore a patentee's ... exclusive position by an award of damages and a permanent injunction. Customers may have established relationships with infringers. The market is rarely the same when a market of multiple sellers is suddenly converted to one with a single seller by legal fiat. Requiring purchasers to pay higher prices after years of paying lower prices to infringers is not a reliable business option.

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Id. at 975-6.

This is the precise situation here. Genencor is establishing itself as a supplier of a competing alpha-amylase enzyme only by infringing Novozymes' '031 patent. If Genencor is permitted to continue this activity, post-litigation market conditions will change so significantly that the market will not readily return to pre-infringement conditions. In addition, the longer that present Novozymes customers can purchase infringing alpha-amylase enzyme products from Genencor, the more difficult it will be for Novozymes to re-establish its pre-infringement market conditions once Genencor's product is permanently enjoined at the conclusion of this litigation. LeFebvre Decl.¶7. Similarly, Genencor's continued infringement will also detrimentally affect Novozymes' pre-infringement reputation. *See Bio-Tech. Gen. Corp. v. Genentech, Inc.* 80 F.3d 1553, 1566 (Fed. Cir. 1996), *cert. denied*, 519 U.S. 911 (1996) (finding patentee would be harmed, in part, because patentee would lose goodwill). LeFebvre Decl.¶8. These injuries cannot be adequately remedied by an award of money damages at the conclusion of trial. *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 1993 U.S. Dist. LEXIS 19959, at *29-30, 28 U.S.P.Q.2d 1362, 1370 (D. Del. July 16, 1993) (finding irreparable harm based on arguments of loss of current dominant market share, loss of prospective business as defendant would attract plaintiff's customers, irreparable harm to good will and reputation as market innovator); *Fisher-Price, Inc. v. Safety 1st, Inc.*, 279 F. Supp. 2d 526, 528 (D. Del. 2003) (permanent injunction in patent case warranted in view of harm to marketplace reputation and loss of market share that could not be quantified in monetary damages); *Motorola Inc. v. Alexander Mfg. Co.*, 786 F. Supp. 808, 815 (N. D. Iowa 1991) (''Money cannot adequately compensate for injury to reputation.'')

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In the absence of a preliminary injunction and return to the *status quo*, it is also likely that more customers will begin to use or switch to Genencor's "me-too" infringing product. If Genencor is permitted to sell its infringing enzyme until a permanent injunction is granted after a full trial, it will be very difficult to return the market to pre-infringement conditions where Novozymes enjoyed a good reputation as a reliable industrial enzyme supplier in general, and a reliable alpha-amylase industrial enzyme supplier in particular. LeFebvre Decl. ¶9; *see Lifescan Inc. v. Polymer Tech. Int'l Corp.*, 1995 U.S. Dist. LEXIS 4916 at *60, 35 U.S.P.Q.2d 1225, 1240 (W.D. Wash. Jan. 3, 1995) (finding irreparable harm where the patentee "is likely to lose goodwill with its customers because of the pricing difference between" the patentee's and the accused infringer's products).

Moreover, requiring Genencor customers to switch to Novozymes' enzyme product *after* imposition of permanent injunctive relief will quite likely result in resentment towards Novozymes, because such a switch will likely impose additional costs to the customers. Because Genencor's enzymes are used in industrial processes that are developed, tested, and scaled-up before they are actually "qualified" by customers for commercial use, the substitution of one supplier's enzyme for another's requires testing and adjusting of the process (different supplier's enzymes may differ to some degree in properties or strengths). Thus, an enzyme user must spend time and money testing and adjusting his process to accommodate a change in suppliers. As a result, enzyme users who purchase Genencor's infringing product will return to Novozymes' products (i) only if necessary, (ii) only with resentment and resistance, and (iii) only at real costs. The resulting damage to Novozymes' goodwill cannot be adequately compensated by an award of money damages at the conclusion of trial. LeFebvre Decl. ¶¶10-11.

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In the words of the Federal Circuit in *Polymer Tech, supra,* this is "not a reliable business option" for either these customers or Novozymes.

2. Novozymes' Damages Are Not Compensable

Genencor's continued infringement will result in price erosion and a loss of market share, customers, and goodwill. Because each is difficult or impossible to calculate, Novozymes' damages cannot be adequately compensated by an award of money damages at the conclusion of trial. *See Critikon, Inc.*, 1993 U.S. Dist. LEXIS 19959, at *29-30, 28 U.S.P.Q.2d at 1370; *Fisher-Price*, 279 F. Supp. 2d at 528; *Drexelbrook Controls, Inc. v. Magnetrol Int'l, Inc.*, 720 F. Supp. 397, 408 (D. Del. 1989) (finding that loss of market share and erosion of customer base, if substantiated, could support finding of irreparable harm); *Jacobson v. Cox Paving Co.*, 1991 U.S. Dist. LEXIS 17787 at *44-51, 19 U.S.P.Q.2d 1641, 1653-55 (D. Ariz. May 20, 1991) (finding a variety of factors can constitute irreparable harm including, loss of market share and price erosion). Similarly, Novozymes' loss of market share and the price erosion on its alpha-amylase product cannot be remedied by an award of money damages. *See Solarex Corp. v. Advanced Photovoltaic Sys. Inc.*, 34 U.S.P.Q.2d 1234, 1240 (D. Del. 1995) (noting that patentee's loss of market share and price erosion contributed to irreparable harm); *see also Spalding & Evenflo Cos. Inc. v. Acushnet Co.*, 1986 U.S. Dist. LEXIS 17129 at *5, 2 U.S.P.Q.2d 1070, 1071 (D. Mass. Nov. 28, 1986) ("Spalding's damages ... (loss of market share, loss of consumer pull and of revenue from non-patented golf product line, etc.) constitute traditional irreparable injury inasmuch as such 'market effects [cannot be] fully compensable in money.'").

In particular, Novozymes has been forced [redacted] to compete with Genencor's infringing product. Novozymes remains under constant price pressure from its customers who have been

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offered the infringing Spezyme Ethyl alpha-amylase product. Damages resulting from this price erosion are incalculable because their effects could last for decades, especially where Novozymes' customers are resistant to any subsequent rise in the price of the alpha-amylase product. LeFebvre Decl. ¶12; *see also Purdue Pharma. L.P. v. Boehringer Ingelheim GmbH*, 98 F. Supp. 2d 362, 397-99 (S.D.N.Y. 2000) (finding price erosion to constitute irreparable harm where damages were incalculable because effects would last for decades and where customers would oppose any increase in price). In addition, price pressure from Genencor has translated into non-compensable lost market share where Novozymes' customers have opted to purchase the infringing Genencor product, instead of the product offered by Novozymes. LeFebvre Decl. ¶13; *see Maitland Co. v. Terra First Inc.*, 1994 U.S. Dist. LEXIS 21597 at *35, 33 U.S.P.Q.2d 1882, 1893 (D.S.C. Aug. 24, 1994) ("loss of market share has itself been recognized as an irreparable injury because it is so difficult to recover"). In fact, [redacted].

Specifically, before Genencor entered the market in April 2004, Novozymes had about [redacted] percent (by sales) of the United States fuel ethanol alpha-amylase market. Since Genencor entered the market, the market share for Liquozyme SC has [redacted] because of Genencor's infringing activities. This trend promises to worsen as long as Genencor's infringing Spezyme Ethyl alpha-amylase product remains on the market. This loss of market share and corresponding price erosion, translates into a significant, immeasurable, and non-compensable loss to Novozymes. LeFebvre Decl. ¶14.

Novozymes' damages are further non-compensable because its lost customers and market share extend beyond the alpha-amylase market. LeFebvre Decl. ¶15; *Stein Indus. Inc. v. Jarco*

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Indus. Inc., 934 F. Supp. 55, 58 (E.D.N.Y. 1996) ("plaintiffs will suffer immeasurable damages due to the loss of customers and the loss of prospective clients.''); *see also A.W. Indus., Inc. v. Electronic Connector Serv. Inc.*, 1997 U.S. Dist. LEXIS 22501 at *19-20, 46 U.S.P.Q.2d 1218, 1224 (S.D. Fla. Nov. 24, 1997) (finding irreparable injury because damages from loss of customers "are not easily susceptible of measurement or quantification"); *Polymer Techs.*, 103 F.3d at 976 (noting that infringing competitors change the marketplace and likelihood exists that customers will establish relationships with the infringers). Commercial enzyme users, at times, purchase several different types of enzymes, rather than a single enzyme. Customers may also prefer to purchase their enzyme needs from as few suppliers as possible to concentrate their buying power and receive the best pricing, supply, and service. It is common in the relevant market here that, when a customer shifts its purchases of one enzyme product from one supplier to another, the purchaser will also seek to shift its purchases of other enzyme products to that new supplier. [redacted], unless defendants' infringing activities are stopped immediately and the previous *status quo* is restored. Because of Genencor's infringing sales of Spezyme® Ethyl, Novozymes has suffered a loss in market share, not just of its Liquozyme SC and Termamyl alpha-amylase enzyme products, but also for its convoyed gluco-amylase enzyme sales LeFebvre Decl. ¶¶16-18.

3. Genencor's Infringement Usurps Novozymes' Statutory Patent Rights

Defendants' infringing activities are unlawfully usurping Novozymes' statutory right to its intellectual property – *i.e.*, Novozymes' right under the '031 patent to exclude others from

making, using, offering for sale, or selling in the United States, or importing into the United States, variant alpha-amylase enzymes as claimed in that patent. Novozymes cannot adequately be remedied by money damages. *H.H. Robertson*, 820 F.2d at 390 ("The nature of the patent grant thus weighs against holding that monetary damages will always suffice to make the patentee whole, for the principal value of a patent is its statutory right to exclude"). As a result, Novozymes presumptively, actually, and statutorily, will suffer irreparable harm in the absence of a preliminary injunction.

Finally, Genencor has begun to sell an infringing food grade Spezyme Ethyl product to the food and beverage industry outside of the U.S. and has begun sampling it to this industry in the U.S. Therefore, it is likely that Genencor will soon begin U.S. sales of its food grade infringing product. Novozymes presently sells its patented Termamyl SC alpha-amylase product to this industry. Genencor's sales of Spezyme Ethyl to the U.S. food and beverage industry will cause irreparable harm to Novozymes in yet another segment of the commercial enzyme business. LeFebvre Decl. ¶25.

C. THE BALANCE OF HARDSHIPS FAVORS NOVOZYMES

Both of Novozymes' alpha-amylase enzyme product lines, Liquozyme SC and Termamyl, were established product lines in the fuel ethanol and starch processing industries prior to the commencement of Genencor's infringing sales. Every day that Genencor is allowed to offer its infringing product, Novozymes suffers irreparable harm that undermines these established product lines. On information and belief, Genencor will not suffer any significant undue hardship if preliminarily enjoined from infringing Novozymes' '031 patent. Genencor sells another alpha-amylase enzyme product (called Spezyme® Fred), and it sells many other

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enzyme products as well. If preliminarily enjoined, Genencor will still have other remaining non-infringing enzyme product lines to sell. LeFebvre Decl. ¶¶19-20.

In addition, there is a significant likelihood that, if Genencor's patent infringement is not preliminarily enjoined, Novozymes will likely continue to suffer irreversible and unfairly precipitated price reductions and loss of market share, not just for its Liquozymes SC *alpha-amylase* enzyme product, but also for its convoyed sales of related *gluco-amylase enzyme* products as well. These products are functionally related because Novozymes' gluco-amylase product is used in a subsequent process step to the use of Novozymes' alpha-amylase product in the making of ethanol. The reduced demand caused by the attendant loss of all such sales could require Novozymes to reduce operations at its sole U.S. plant, based in Franklinton, North Carolina, that domestically produces its Liquozymes SC product, where Novozymes is the largest employer (about 400 jobs) and driver of the local economy. LeFebvre Decl. ¶¶26-27.

On another level of the balancing of hardships factor, Genencor remained on the market even after it learned that Novozymes' allowed patent application (which led to the '031 patent) would cover Genencor's alpha-amylase enzyme product upon issuance of the patent. This was so because on September 29, 2004 Novozymes voluntarily gave Genencor a copy of the allowed patent claims from the application in the hope that Genencor would see the fruitlessness of continuing to sell its product. LeFebvre Decl. ¶28. Unfortunately, Genencor saw it differently and "balanced" its own risk by continuing its activities. Now, therefore, it is too late for Genencor to argue that the "equities" tip in its favor.

In sum, the balance of the hardships factor weighs in Plaintiff's favor.

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D. THE REQUESTED PRELIMINARY INJUNCTION WOULD NOT ADVERSELY AFFECT THE PUBLIC INTEREST

When "patent rights will be flagrantly violated," the public interest is best served by the protection of those rights. *H.H. Robertson*, 820 F.2d at 391 (affirming grant of preliminary injunction); *see also Solarex Corp.*, 34 U.S.P.Q.2d at 1241 ("The public has an interest in upholding and preserving patent rights ...."). "[T]he focus of a district court's public interest analysis should be whether there exists some critical public interest that would be injured by the grant of preliminary relief." *eSpeed, Inc.*, 2004 U.S. Dist. LEXIS 385, at *7-9, 69 U.S.P.Q.2d at 1469 (quoting *Hybritech*, 849 F.2d at 1458); *Drexelbrook Controls*, 720 F. Supp. at 408.

Novozymes is not aware of any "critical public interest that would be injured by the grant of [the requested] preliminary relief." However, the public interest of the people in Franklinton, North Carolina, may be adversely affected if the preliminary injunction is NOT granted. In particular, although the Franklinton plant makes *both* alpha-amylase *and* gluco-amylase enzyme products and only about [redacted]% of the plant is devoted *solely* to alpha-amylase production, the continued loss of Novozymes' business (and profits) for both product lines could adversely affect employment opportunities at the plant. LeFebvre Decl. ¶29.

Accordingly, the public policy factor also weighs in favor of Novozymes.

V. CONCLUSION

Each factor this Court must consider to grant Plaintiff's request for preliminary injunctive relief – the likelihood of success on the merits, irreparable harm in the absence of an injunction, a balancing of the hardships, and the public interest – weighs in Plaintiff's favor. Accordingly, for the foregoing reasons, Plaintiff requests that its underlying motion for a preliminary injunction be granted.

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Respectfully submitted,

/s/

Dated: June 22, 2005

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CERTIFICATE OF SERVICE

I, Richard H. Morse, hereby certify that on June 22, 2005, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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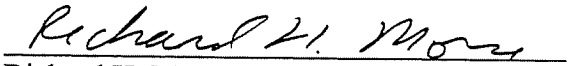

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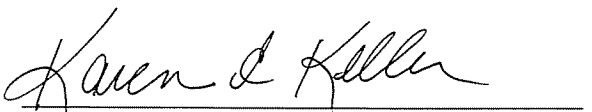

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